Modern technologies for glucose monitoring and insulin replacement

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Abstract

Self-monitoring of blood glucose (SMBG) is an integral part of diabetes care, allowing patients to identify patterns, calculate doses and identify hypoglycaemic or hyperglycaemic excursions. Structured education on interpretation of the results and algorithms to calculate insulin doses, structured and automated approaches to pattern recognition, and automation of data collection through these devices can contribute to improved glycaemic control.

Insulin delivery has not changed much since it was first used in 1921. Although therapy has moved from impure animal insulins to genetically modified rapid- and long-acting analogues, the mode of insulin delivery through subcutaneous injections remains the same. With the increasing use of continuous subcutaneous insulin infusions (CSII) or insulin pumps, greater precision in delivery is possible, but recent advances such as intraperitoneal insulin delivery and the combination of continuous glucose monitoring with insulin pumps, using algorithms to produce closed-loop systems, herald a new future for insulin delivery.

Keywords CGM; continuous glucose monitoring; continuous subcutaneous insulin infusions; CSII; insulin pumps; insulin therapy; self-monitoring of blood glucose; SMBG

Intermittent glucose monitoring

Although glucose has been identified in urine as a symptom of diabetes mellitus for centuries, its quantification became possible only in 1908 with the development of Benedict's reaction. The first home urine monitoring system [Clinitest® strips] became available around 1945, but plasma glucose became measurable only during the mid 1950s after development of glucose oxidase-based systems. It was not till 1980 that the first portable home glucose monitoring systems were developed.[1] Current meters require very small volumes of capillary blood [0.30–1.50 μL] and provide readings within 5 seconds. They calculate glucose concentration based on enzymatic reactions that are generally dependent on either glucose oxidase (GOX) or glucose dehydrogenase (GDH). GOX meters can be affected by ambient oxygen concentrations, while GDH systems can be affected by other sugars such as maltose xylose and icodextrin [found in peritoneal dialysate]. Several other drugs, including ascorbic acid, paracetamol, dopamine and mannitol, can also interfere with both GDH and GOX based devices. Most meters have a large memory, which can be used to download readings to spreadsheets or proprietary software, making the data much more accessible for pattern recognition. From 2014, meters will have to adhere to new ISO guidelines that require 95% of readings to be within 0.83 mmol/L (15 mg/dL) of the gold standard. It is important to remember that capillary glucose meters read whole blood, and then are calibrated to produce a 'plasma equivalent' glucose reading, assuming a normal haematocrit. Apart from haematocrit, hypertriglyceridaemia and paraproteinaemia can also affect the technical accuracy of blood glucose readings by causing pseudohypoglycaemia.

New developments

- Bolus advisors: Despite being taught how to adjust insulin dosage based on carbohydrate intake [using insulin to carbohydrate ratios] and current glucose concentrations [using insulin sensitivity factors] patients miscalculate rapid-acting insulin doses more than 50% of the time.[2] Some newer meters can be pre-programmed with these ratios, and can perform these calculations for the patient. Initial studies showed significant reductions in HbA_{1c}.[3]
- Pattern recognition: Some meters and download software can analyse glucose readings and identify patterns of recurrent hypoglycaemia or hyperglycaemia.[4]
- Connectivity: Meters are now offering connectivity to insulin pumps, making it easier for patients to react to readings. They can also connect to mobile phones, and through these to cloud-based databases.

Continuous glucose monitoring (CGM)

CGM allows almost continuous display of glucose measured from the interstitial fluid using small sensors (coated with glucose oxidase) placed subcutaneously. They generate a current proportional to glucose concentrations, which can be read as a glucose value. However, interstitial glucose lags approximately 10–15 minutes behind plasma glucose, and this lag increases with increased rate of change.[5] This can mean that concurrent readings from CGM devices and capillary glucose meters are quite likely to be slightly different, and patients often feel that the CGM devices have missed the event, especially when patients rapidly drop into hypoglycaemia. CGM can be used over 7 days as a diagnostic tool, often with data blinded from the patient to identify patterns, and as a guide for adjusting therapy. They can also be used therapeutically by patients, who can use the real-

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time information of glucose, including direction and rate of change, and respond to alarms if glucose falls outside pre-set thresholds.[6] Some of these devices can 'pair' with insulin pumps, allowing display of glucose on the insulin pump, and in the case of the Medtronic Veo®, allow the pump to suspend insulin delivery for up to 2 hours if the patient fails to respond to a 'hypoglycaemia' alarm (termed low-glucose suspend [LGS]).[7] Key issues with currently available CGM relate to the accuracy and longevity of the sensors. Current sensors have approximately 80% sensitivity and specificity for hypoglycaemia.[8]

New developments

- Novel sensors: fluorescent based sensors are currently under trial which aim to offer a longer duration of use, or provide redundancy and better fault detection to improve reliability.[9]
- Closed-loop platforms: there are a number of systems in clinical trials which use algorithms to use the sensor glucose values and modulate insulin delivery. Current versions have shown efficacy in increasing time in target overnight, with almost complete avoidance of nocturnal hypoglycaemia, and some benefits through the day as well.[10]

Insulin delivery

Insulin is delivered by subcutaneous injection using syringes, pens or insulin pumps. When injected through the skin, insulin is delivered into the systemic circulation, rather than into the portal circulation as in physiology, which means that it is almost impossible to mimic completely normal physiology.

Animal insulin: porcine (pork) insulin has one amino acid and bovine (beef) insulin has three amino acids different from human insulin. From the late 1930s, protamine and zinc were added to the insulin suspension to increase the duration of action (the effects of lente and ultralente insulin lasted between 18 and 36 hours). These preparations are now largely obsolete, although neutral protamine Hagedorn insulin (NPH), developed in the 1950s, is still widely used.

Human insulin: insulin was the first peptide to be sequenced and the first peptide to be generated using recombinant DNA technology. When human insulin was first introduced a number of patients complained of loss of warning signs of hypoglycaemia, and rapid unpredictable hypoglycaemia. Even though no difference was ever shown in controlled studies, many of these patients have continued to use animal insulin.

Analogue insulin: insulin exists in solution as hexamers held together by a zinc molecule. The rate of dissociation into monomers after injection into the subcutaneous tissue determines the speed of onset and duration of action. Making some alterations to the amino acid sequence of insulin can speed up the onset of action; this has led to development of rapid-acting

Insulin types and action profiles

Insulin preparations	Manufacturer	Type	Onset	Peak	Effective duration
Rapid-acting			**5–15 min**	**1 h**	**2–4 h**
Insulin aspart (Novorapid®)	Novo Nordisk	analogue	5–15 min	30–90 min	3–5 h
Insulin lispro (Humalog®)	Eli Lilly	analogue	5–15 min	30–90 min	4–6 h
Insulin glulisine (Apidra®)	Sanofi-Aventis	analogue	20 min	60–90 min	3–5 h
Short-acting			**30 min**	**2–4 h**	**6–8 h**
Actrapid	Novo Nordisk	human	30–60 min	2–3 h	6–8 h
Humulin S	Eli Lilly	human	30–60 min	2–3 h	6–8 h
U-500 Regular insulin	Eli Lilly	human	30–60 min	4–8 h	Up to 12 h
Intermediate			**30 min**	**4–8 h**	**14–16 h**
Insulatard[a]	Novo Nordisk	human	2–4 h	4–10 h	10–16 h
Humulin I	Eli Lilly	human	2–4 h	4–10 h	10–16 h
Long-acting; Basal			**1–4 h**	**Peakless**	**18–24 h**
Insulin detemir (Levemir®)	Novo Nordisk	analogue	0.8–2 h	3–9 h (to peak action)	16–20 h
Insulin glargine (Lantus®)	Sanofi-Aventis	analogue	2–4 h	4 h (to peak action)	16–20 h
Insulin degludec (Tresiba®)	Novo Nordisk	analogue	1–2 h	8–12 h	Up to 42 h
Pre-mixed insulin	**Variable depending on mixture**				
NovoMix30 70/30[b]	Novo Nordisk	analogue	5–15 min	2–12 h	10–16 h
Humulin M3[c]	Eli Lilly	analogue	5–15 min	Dual	10–16 h
HumalogMix25 75/25[d]	Eli Lilly	analogue	5–15 min	30–90 min	10–16 h
HumalogMix50 50/50[e]	Eli Lilly	analogue	5–15 min	3–5 h	10–16 h

[a] Pork insulatard is also available.
[b] 30% aspart and 70% Protamix-crystallized aspart.
[c] 30% soluble insulin, 70% isophane.
[d] 25% lispro and 75% neutral protamine lispro.
[e] 50% lispro and 50% neutral protamine lispro.

Table 1

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